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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,134	10/10/2003	Hal S. Padgett	1328-005	1176

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	**Application No.** 10/684,134	**Applicant(s)** PADGETT ET AL.	
	Examiner Amanda M. Shaw	**Art Unit** 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-12,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 30, 2006 has been entered.

Claims 1-2, 4-12, and 42-43 are currently pending. Claims 1, 7, 9, 10, 42 and 43 have been amended. Therefore Claims 1-2, 4-12, and 42-43 will be addressed herein.

Information Disclosure Statement

2. The listing of references in the specification (Pages 43-47) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

3. The drawings are objected to under 37 CFR 1.83(a) because the description of the figures in the specification fails to show the corresponding SEQ ID NO for the sequences in Figures 1-2.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-6, and 8-12 are indefinite over the recitation of the phrase "preparing at least one heteroduplex between said at least said two parent polynucleotides, cleaving at least one polynucleotide strand in said heteroduplex at a mismatch site with an effective amount of mismatch directed strand cleavage activity to form a cleavage site, replacing at least one nucleotide on at least one polynucleotide strand at or near the cleavage site". This phrase in considered indefinite because it is unclear how these steps accomplish making a polynucleotide wherein the polynucleotide has a different nucleotide sequence from either of said at least two parent polynucleotides or the complementary sequences of said at least two parent polynucleotides. It seems like in order for this method to work the heteroduplex must contain at least two mismatch sites. Further the cleaving step would have to be effected on both strands of the heteroduplex wherein at any particular mismatch it is random as to which strand is repaired.

Claim 6 is indefinite over the recitation of the phrase "the heteroduplex polynucleitde sequence". There is insufficient antecedent basis for this limitation in the claim. Further it is unclear how this claim further limits claim 1. For example it is unclear if claim 6 requires the polynucleotide molecule of greater than about 100 bp or if this just describes the origin of the heteroduplex polynucleotde seuqnece.

Claim 7 is indefinite over the recitation of the phrase "preparing at least two heteroduplexes between said at least said three parent polynucleotides, cleaving at least one polynucleotide strand in said heteroduplex at a mismatch site with an effective amount of mismatch directed strand cleavage activity to form a cleavage site, replacing at least one nucleotide on at least one polynucleotide strand at or near the cleavage site". This phrase in considered indefinite because it is unclear how these steps accomplish making a polynucleotide wherein the polynucleotide has a different nucleotide sequence from either of said at least three parent polynucleotides or the complementary sequences of said at least three parent polynucleotides. It seems like in order for this method to work the heteroduplexes must contain at least two mismatch sites. Further the cleaving step would have to be effected on both strands of the heteroduplex wherein at any particular mismatch it is random as to which strand is repaired.

Claim 42 is indefinite over the recitation of the phrase " mixing copies of the heteroduplex polynucleotide sequence with an effective amount of mismatch-directed strand cleavage activity, proofreading activity, and ligase activity; and allowing sufficient time for a number of non-complementary nucleotide base pairs to be converted to complementary base pairs, wherein a diverse population of polynucleotide sequences results, wherein at least one polynucleotide sequence in said diverse population is not identical to said heteroduplex polynucleotide sequence or the complementary sequence of said heteroduplex polynucleotide". This phrase in considered indefinite because it is unclear how these steps accomplish making a population of sequence variant from a heteroduplex polynucleotide sequence where said heteroduplex polynucleotide sequence has at least two non-complementary nucleotide base pairs. It seems like in order for this method to work the cleaving step would have to be effected on both strands of the heteroduplex wherein at any particular mismatch it is random as to which strand is repaired. Additionally it is noted that the claims do not actually require mixing with, e.g. an agent having mismatch directed strand cleavage activity, proofreading activity, and ligase activity. For example things like cleavage could be caused by, e.g. irradiation, etc. In this case it is unclear how one would mix copies of a polynucleotide with irradiation.

Claim 43 is indefinite over the recitation of the phrase " preparing at least one heteroduplex polynucleotide sequence; mixing copies of the heteroduplex polynucleotide sequence with an effective amount of mismatch-directed strand cleavage activity, proofreading activity, and ligase activity; allowing sufficient time for the percentage of complementarity between strands of the heteroduplex polynucleotide sequence to increase, wherein a diverse population of polynucleotide sequences results, wherein at least one polynucleotide sequence in said diverse population is not identical to said heteroduplex polynucleotide sequence or the complementary sequence of said heteroduplex polynucleotide, and screening or selecting said population of variants for said desired functional property". This phrase in considered indefinite because it is unclear how these steps accomplish obtaining a polynucleotide sequence encoding a desired functional property. It seems like in order for this method to work the heteroduplex must contain at least two mismatch sites. Further the cleaving step would have to be effected on both strands of the heteroduplex wherein at any particular mismatch it is random as to which strand is repaired. Additionally it is noted that the claims do not actually require mixing with, e.g. an agent having mismatch directed strand cleavage activity, proofreading activity, and ligase activity. For example things like cleavage could be caused by, e.g. irradiation, etc. In this case it is unclear how one would mix copies of a polynucleotide with irradiation.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 6-12, and 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Arnold et al (WO 99/29902).

Regarding Claims 1 and 42 Arnold et al teach a method comprising: preparing a heteroduplex between two polynculeotide sequences which contain regions of similarity with each other but also have at least two mismatches, and exposing the heteroduplex to enzymes of a DNA repair, and optionally a replication system, that repairs unmatched pairings. Arnold et al further teach that the exposing step can be performed in vitro or in vivo. The exposing step results in DNA repair at bulges in the heteroduplexes due to DNA mismatching. The DNA repair process is typically effected on both component strands of a heteroduplex molecule and at any particular mismatch is typically random as to which strand is repaired. The resulting population can thus contain recombinant polynucleotides encompassing an essentially random reassortment of points of divergence between parental strands (Pages 9 and 10). Arnold et al do not specifically state that after the DNA repair process at least one of the polynucleotide strands has a nucleotide sequence not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides. However it is a property of the method of Arnold et al that it could result in having at least one of the polynucleotide strands has a nucleotide sequence not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides. For example if one parent had the sequence of AT*C*GCTAGC*A*C and the second parent had the sequence of TA*T*CGATCG*G*G and these two strands formed a heteroduplex and were exposed to a DNA repair enzymes, wherein the DNA repair process it typically effected on both component strands of a heteroduplex molecule and at any party mismatch is typically random as to which strand is repairs, then the first parent strand could potentially cleave at the position shown in bold AT**C**GCTAGCAC and the second parent strand could potentially cleave at the position shown in bold TATCGATCG**G**G. After replacing the nucleotides on each strand the first strand would have the sequence ATAGCTAGCAC and the second strand would have the sequence TATCGATCGTG. Thus the method of Arnold et al is capable of producing polynucleotides that are not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides

Regarding Claim 2, Arnold et al teach that the heteroduplexes formed may be an open circular heteroduplex (Page 13).

Regarding Claim 4, Arnold et al teach that the parent polynucleotides can encode variant forms of a plurality of genes constituting a multigene pathway (Page 11).

Regarding Claim 6, Arnold et al teach that the polynucleotide sequences which form the heteroduplex can be 50, 250, 1000, 10,000, 100,000 or more bases (Page 11).

Regarding Claim 7 Arnold et al teach that the method can be performed with at least 3 parent polynucleotides. Specifically Arnold et al teach that the method can be performed with two, 10, 100, 1000 etc parent polynucleotides (Pages 10 and 13).

Regarding Claim 8, Arnold et al teach that a plurality of variant polynucleotides are formed. Specifically Arnold et al teach that the heteroduplex can be exposed to a replication system. It is inherent that replicating the heteroduplex will produce multiple copies of the variant (Page 9).

Regarding Claim 9 and 43 Arnold et al teach a method for evolving a polynucleotide toward acquisition of a desired property. The method comprises: preparing a heteroduplex between two polynucleotide sequences which contain regions of similarity with each other but also have at least two mismatches, and exposing the heteroduplex to enzymes of a DNA repair, and optionally a replication system, that repairs unmatched pairings. Arnold et al further teach that the exposing step can be performed in vitro or in vivo. The exposing step results in DNA repair at bulges in the heteroduplexes due to DNA mismatching. The DNA repair process is typically effected on both component strands of a heteroduplex molecule and at any particular mismatch is typically random as to which strand is repaired. The resulting population can thus contain recombinant polynucleotides encompassing an essentially random reassortment of points of divergence between parental strands. The resulting polynucleotides are then screened or selected for a desired property. The property can be a property of the polynucleotide per se, such as capacity of a DNA molecule to bind to a protein or can be a property of an expression product thereof, such as mRNA or a protein (Pages 9 and 10). Arnold et al do not specifically state that after the DNA repair process at least one of the polynucleotide strands has a nucleotide sequence not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides. However it is a property of the method of Arnold et al that it could result in having at least one of the polynucleotide strands has a nucleotide sequence not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides. For example if one parent had the sequence of AT*C*GCTAGC*A*C and the second parent had the sequence of TA*T*CGATCG*G*G and these two strands formed a heteroduplex and were exposed to a DNA repair enzymes, wherein the DNA repair process it typically effected on both component strands of a heteroduplex molecule and at any party mismatch is typically random as to which strand is repairs, then the first parent strand could potentially cleave at the position shown in bold

AT**C**GCTAGCAC and the second parent strand could potentially cleave at the position shown in bold TATCGATCG**G**G. After replacing the nucleotides on each strand the first strand would have the sequence ATAGCTAGCAC and the second strand would have the sequence TATCGATCGTG. Thus the method of Arnold et al is capable of producing polynucleotides that are not identical to either of the parent polynucleotides or the complementary sequences of the polynucleotides

Regarding Claim 10 Arnold et al teach that a second heteroduplex comprising at least one variant strand can be formed and the process can be repeated. Specifically Arnold et al teach that the variants can be subjected to further rounds of recombination using the heteroduplex procedures (Page 18).

Regarding Claims 11 and 12 Arnold et al teach that the variant polynucleotides can be converted to RNA and be translated prior to screening and selecting. Specifically Arnold et al teach that the variant polynucleotides (DNA) as well as their expression products or secondary metabolites produced by their expression products are isolated a screened for the desired property (Page 18). In order for the expression products to analyzed, the DNA would have had to been converted to RNA and then translated.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al (WO 99/29902) in view of Wetmur (US Patent 5877280).

The teachings of Arnold et al are presented above in paragraph 5.

Regarding Claim 5, Arnold et al do not teach a method wherein the heteroduplex polynucleotide sequence is a genome.

However, Wetmur et al teaches a method called genome mismatch scanning. This method created for whole genome scanning utilizes E. coli MutS and the other enzymes of the mismatch repair system to detect differences between two strands of oligonucleotides (Column 12).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Arnold et al to an entire genome. One would have been motivated to do so in order to detect differences between two genomes which can then be applied towards genome mapping and or cloning genes based on sequence differences or similarities between the two genomes.

Terminal Disclaimer

7. The terminal disclaimer filed on November 30, 2006 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on Application Numbers: 10066390, 10280913, or 10637758 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

8. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

Diana
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PRIMARY EXAMINER